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REVIEWS

Heart crosstalk with other organs and pharmacological strategies for cardioprotection

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[Abstract] Cardiovascular disease (CVD) is the leading cause of death worldwide. It has been recognized that specific regulatory factors from peripheral tissues can influence the pathological progression of atherosclerosis, myocardial infarction (MI) and heart failure (HF). Drugs targeting the regulation of pathways related to hepatic lipid metabolism, intestinal flora, renal sodium excretion and hypoglycemia, bone marrow clonal hematopoiesis and immune inflammation, such as Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, Sodium-glucose Cotransporter-2 (SGLT2) inhibitors, IL-1β monoclonal antibodies and Chimeric antigen receptor (CAR) -T therapy, have been shown to have significant protective effects in the prevention and treatment of cardiovascular disease, especially ischemic heart disease and HF. Various forms of interaction between cardiovascular system diseases and cerebrovascular, liver and intestinal metabolism, kidney and other functional disorders have been widely reported. In this review, we focus on the interactions between the cardiovascular system and other organs in ischemic heart disease and HF, highlight novel therapeutic strategies that modulate cardiometabolic and inflammatory processes.

[Key words] Cardiovascular diseases; Multiple organ; Crosstalk; Therapeutic target; Cardioprotection

1 Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide. Although reperfusion is successful in reducing infarct size and improving overall prognosis, ischemic heart diseases including myocardial infarction (MI) remain at increased risk of heart failure (HF)[1]. It has been recognized that specific regulatory factors from peripheral tissues can influence the pathological progression of atherosclerosis, MI and HF. For instance, the lipid metabolism in liver and absorption in intestine regulate cholesterol and triglyceride levels and affect the progression of atherosclerosis and MI. Renal dysfunctions strongly affect the progression and prognosis of CVD[2]. In response to myocardial ischaemia, hematopoietic stem cells (HSC) in the bone marrow are induced to generate a variety of inflammatory myeloid cells, followed by recruiting to arterial wall or myocardium[3]. The association between lymphocyte-dominated adaptive immunity and atherosclerosis and MI, however, remain less clear and worth further explored[4-5]. Cardiac injury

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is common in patients with cerebrovascular disease and brain-heart interaction was well discussed by reviewed previously[6]. In this Review, we provide an overview of the interactions between the cardiovascular system and other organs in ischemic heart disease and HF. We highlight the new therapeutic targets in preclinical and clinical development, including PCSK9 inhibitors, SGLT2 inhibitors, IL-1β monoclonal antibodies and Chimeric antigen receptor (CAR) -T therapy, which are novel therapeutic strategies that modulate cardiometabolic and inflammatory processes.

2 Liver, gut and blood vessel

The genetic association between cholesterol and MI was first made in 1939[7]. Hepatic lipid metabolism and intestinal cholesterol absorption regulate cholesterol and triglyceride levels and affect the progression of atherosclerosis and acute MI (Fig.1). As the cholesterol-lowering drugs, the discovery of statins greatly contributes to prevention of atherosclerosis and MI. Given that statins effectively control cholesterol level and reduce cardiovascular morbidity via regulating lipid metabolism, side effects including statin-associated muscle symptoms, hepatotoxicity, renal toxicity occasionally lead to statin discontinuation and limit the clinical applications of this class of drugs. Observational studies suggested that 10%-15% of patients are intolerant to statins[8]. Proprotein convertase subtilisin/kexin type 9 (PCSK9) represents a novel therapeutic target in the management of dyslipidemias[9]. PCSK9, secreted by liver, interacts with low-density lipoprotein receptor (LDL-R) and activates its degradation. It reduces the absorption of low-density lipoprotein cholesterol (LDL-C) by cells, and accelerates the accumulation of LDL-C in blood vessel walls.

In clinical trials involving patients with high LDL-C levels, anti-PCSK9 monoclonal antibodies including evolocumab[10] and alirocumab[11] reduced LDL-C levels by more than 60% and significantly reduced cardiovascular events. For atherosclerotic patients who are intolerant to statins, PCSK9 inhibitors bring notable clinical benefits, reducing the risk of myocardial infarction, stroke and unstable angina.

Intestinal microbiota also contributes to metabolic health and, when abnormal, may lead to several metabolic disorders including CVD[12]. For instance, the gut microbiota generated trimethylamine *N*-oxide (TMAO) directly contributes to platelet hyperactivity, which is associated with a higher risk of arterial thrombosis[13]. In human subjects, elevated TMAO levels predict incident risk for thrombotic events.

3 Kidney and heart

Another organ which correlates closely with cardiovascular diseases is the kidney. Renal dysfunctions strongly affect the progression and prognosis of CVD. More than 60% of patients with chronic kidney disease (CKD) simultaneously suffer from cardiovascular diseases. Likewise, 40%-50% of patients with heart failure have renal dysfunction concurrently[2]. The severity of CVD is also highly correlated to the severity of CKD. Because heart function has a very common interaction with kidney function, the term of "cardio-renal syndrome" has been proposed to describe the condition in which either heart or kidney is dysfunctional, the condition induces the dysfunction of the other organ[14]. Current studies suggest that the crosstalk of CVD and renal dysfunctions is due to multiple mechanisms including hemodynamics, activation of the renin-angiotensin-aldosterone (RAAS) system, activation of the sympathetic nervous system (SNS) and excessive inflammation (Fig. 1). In terms of hemodynamic mechanism, when renal function is damaged, the decrease of glomerular filtration rate (GFR) causes renal hypertension, which increases the load of heart and continuously damages the heart, eventually causes adverse cardiovascular

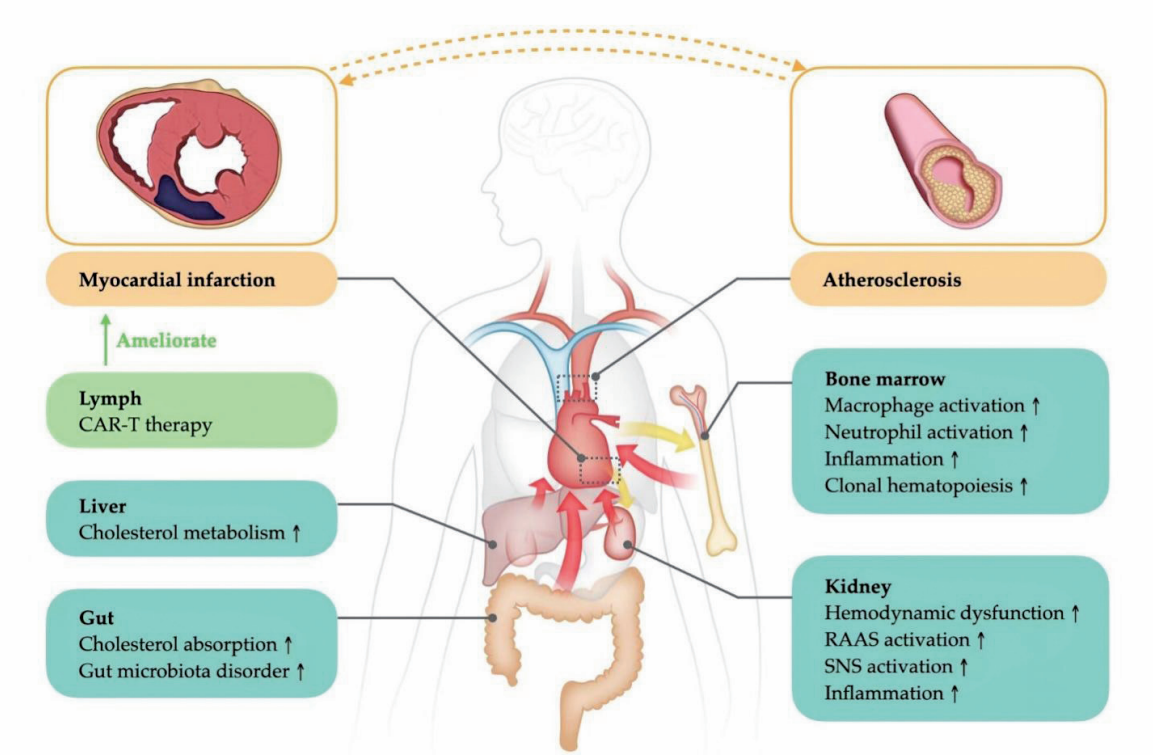

Fig. 1 Multi-organ crosstalk contribute to atherosclerosis and ischemic heart disease

events. In turn, in the heart failure setting, the dysfunctional pumping capacity of the heart leads to an increase in renal venous pressure and a decrease in net filtration pressure. Glomeruli and tubules are then continuously damaged, resulting in a decrease in GFR and progression of CKD[2].

3.1 SGLT2 inhibitors

Sodium-glucose Cotransporter-2 (SGLT2) is expressed mainly in proximal convoluted tubular epithelial cells and reabsorbs of >90% of filtered glucose. When SGLT2 is inhibited, the reabsorption of glucose in the renal tubule is suppressed and the blood glucose level is reduced accordingly. Surprisingly, a series of clinical trials showed that SGLT2 inhibitors including empagliflozin[15-17], dapagliflozin[18-19] and canagliflozin[20] all exhibited cardioprotection effects in addition to their hypoglycemic effects. Even for heart failure in patients without diabetes, SGLT2 inhibitors still significantly reduce heart failure hospitalization and mortality. Moreover, SGLT2 inhibitors significantly reduce the risk of GFR reduction and end-stage renal disease in CKD patients, regardless of diabetes[21]. Hence, SGLT2 inhibitors are considered to have triple protective effects on blood glucose, heart and kidney. The potential mechanisms by which SGLT2 inhibitors exert direct myocardial beneficial effects include promoting sodium excretion to reduce plasma volume and improve vascular function, shifting metabolic pathways to ketone metabolism in the heart and kidney, reducing inflammation and the production of inflammatory cytokines, etc[22]. In addition to the indirect cardioprotective effects via the kidney, SGLT2 inhibitors also directly act on other targets of cardiomyocytes and play a direct cardioprotective role through mechanisms including autophagy and autosis[23].

4 Bone marrow and heart

In response to pathogens or environmental injury (such as myocardial ischaemia or hemodynamic overloading), hematopoietic

stem cells (HSC) in the bone marrow activate to produce a variety of inflammatory myeloid cells, which invade into arterial wall or myocardium. In most cases, excessive inflammatory cells are detrimental, exacerbating atherosclerosis progression and myocardial infarction injury[24]. During the pathological progression of atherosclerosis, inflammatory signals mobilize inflammatory monocytes to invade into atherosclerosis-prone areas where cholesterol accumulated, the monocytes differentiate into macrophages and thereafter, lipid-rich mast cells after they ingest cholesterol. The cells then undergo different forms of cell death, and necrotic lipid core would form from the dead cells and accumulate to form plaques, which meanwhile trigger further inflammation, and eventually exacerbate atherosclerosis progression[24]. In the onset of MI, a large number of cardiomyocytes are damaged or died in a short time. The damaged cardiomyocytes release a series of danger signals, which trigger downstream inflammatory responses to remove residues of dead cells. Within days or even hours, numerous inflammatory cells including macrophages[25] and neutrophils[26] are recruited to the infarcted heart. Inflammation in one way helps to remove the residues of necrotic cells and extracellular matrix, on the other hand, excessive inflammation further aggravates the death of cardiomyocytes and cardiac remodelling, thus further exacerbates myocardial injury. The most important inflammatory pathway associated with cardiovascular diseases is the NOD-like-receptor: pyrin containing domain 3 (NLRP3) inflammasome signaling pathway[27]. The activation of NLRP3 pathway is primed by the recognition of sterile damage-associated molecular patterns (DAMP) via pathogen recognition receptors, the activation of NLRP3 pathway eventually results in the secretion of the proinflammatory cytokine IL-1β, which triggers a series of cascades and exacerbates inflammation damage.

4.1 Clonal hematopoiesis

Inflammatory responses also drive the clonal hematopoiesis of HSC. Clonal hematopoiesis refers to a condition in which one single HSC proliferates to a large clone and this clone eventually reaches a larger proportion in blood cell population[28]. Clonal hematopoiesis caused by some certain mutations may lead to higher CVD risk. Genetic studies have shown that mutations in genes including *DNMT3A*, *TET2*, *ASXL1* and *JAK2* are highly associated with coronary heart disease[29-31]. *JAK2* mutation carriers have the highest risk of coronary heart disease[29], while *TET2* mutation carriers have a very high risk of premature MI[31]. Interestingly, *TET2* mutation exacerbates atherosclerosis and HF because this mutation causes high activation of NLRP3 pathway in macrophages, leading to excessive release of IL-1β[30-31].

4.2 IL-1β and GSDMD

Data from the CANTOS (canakinumab antiinflammatory thrombosis outcome study) trial showed that canakinumab, an anti-IL-1β monoclonal antibody, reduced cardiovascular events and all-cause and cardiovascular mortality significantly[32].Unfortunately, FDA rejected to approve canakinumab for cardiovascular indications, a major possible reason is that only patients with a C-reactive protein (CRP) level of higher than 2 mg/L are enrolled in the trial, which makes it doubtful that whether canakinumab has cardiovascular benefits in a broader patient spectrum. At present, no drugs targeting inflammatory cells and their products to treat cardiovascular indications have been approved. This fact implies that many unsolved problems still exist in the field of immunotherapy for CVD. For example, could other factors in the NLRP3 pathway be therapeutic targets? What are the roles of different types of cells during cardiovascular inflammation? Our recent work demonstrated that

gasdermin D (GSDMD), which mediates IL-1β secretion after NLRP3 activation, plays a crucial role in neutrophils and regulates acute myocardial infarction injury[33]. This along with many other studies hinted the possibility of exploring novel targets to reduce cardiovascular inflammation damage. As a matter of fact, several drugs targeting the NLRP3 pathway besides IL-1β are under development[34-36].

5 The lymphatic system and heart

While the link between innate immunity and CVD is well established, the association between lymphocyte-dominated adaptive immunity and atherosclerosis and MI, however, is much less clear and worth further explored[4-5]. Chimeric antigen receptor (CAR) -T therapy harnesses the power of adaptive immunity, engineering endogenous T cells for immunotherapy[37]. A recent study modified T lymphocytes with an antifibrotic CAR, the engineered CAR-T cells hence specifically eliminate the proliferating fibroblasts and ameliorate cardiac remodelling after ischemic injury[38-39]. This study explored the possibility of the cutting-edge CAR-T technique beyond oncology therapy and shed light on the novel strategy for CVD therapy.

6 Conclusion

Multiple organs and tissues including liver, gut, kidney and bone marrow profoundly affect the development and progression of CVD such as atherosclerosis and MI through metabolic and/or inflammatory pathways. The progression of atherosclerotic plaque increases the risk of acute MI, while acute myocardial ischemic injury also accelerates the development of atherosclerosis[40]. We acknowledge the concept that CVD are systematic diseases, the in-depth investigation on multi-organ crosstalk will provide insight for understating the pathophysiological of ischemia heart diseases and novel strategy for management of CVD.

7 Conflicts of interest

These authors have no conflict of interest to declare.

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References

[1] Heusch G. Myocardial ischaemia-reperfusion injury and cardioprotection in perspective[J]. *Nat Rev Cardiol*, 2020, 17(12):773-789.

[2] Schefold JC, Filippatos G, Hasenfuss G, et al. Heart failure and kidney dysfunction: epidemiology, mechanisms and management[J]. *Nat Rev Nephrol*, 2016, 12(10):610-623.

[3] Libby P. The changing landscape of atherosclerosis[J]. *Nature*, 2021, 592(7855):524-533.

[4] Hofmann U, Frantz S. Role of lymphocytes in myocardial injury, healing, and remodeling after myocardial infarction[J]. *Circ Res*, 2015, 116(2): 354-367.

[5] Saigusa R, Winkels H, Ley K. T cell subsets and functions in atherosclerosis[J]. *Nat Rev Cardiol*, 2020, 17(7):387-401.

[6] Chen Z, Venkat P, Seyfried D, et al. Brain-heart interaction: cardiac complications after stroke[J]. *Circ Res*, 2017, 121(4):451-468.

[7] Turner KB, Steiner A. A long term study of the varivation of serum cholestrol in man [J]. *J Clin Invest*, 1939, 18(1):45-49.

[8] Ward NC, Watts GF, Eckel RH. Statin toxicity[J]. *Circ Res*, 2019, 124(2):328-350.

[9] Sabatine MS. PCSK9 inhibitors: clinical evidence and implementation[J]. *Nat Rev Cardiol*, 2019, 16(3): 155-165.

[10] Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease[J]. *N Engl J Med*, 2017, 376(18):1713-1722.

[11] Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome[J]. *N Engl J Med*, 2018, 379(22):2097-2107.

[12] Witkowski M, Weeks TL, Hazen SL. Gut microbiota

and cardiovascular disease[J]. *Circ Res*, 2020, 127(4):553-570.

[13] Zhu W, Gregory JC, Org E, et al. Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk[J]. *Cell*, 2016, 165(1):111-124.

[14] Rangaswami J, Bhalla V, Blair JEA, et al. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association[J]. *Circulation*, 2019, 139(16):e840-e878.

[15] Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure[J]. *N Engl J Med*, 2020, 383(15):1413-1424.

[16] Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction[J]. *N Engl J Med*, 2021, 385(16):1451-1461.

[17] Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes[J]. *N Engl J Med*, 2015, 373(22):2117-2128.

[18] McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction[J]. *N Engl J Med*, 2019, 381(21):1995-2008.

[19] Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes[J]. *N Engl J Med*, 2019, 380(4):347-357.

[20] Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes[J]. *N Engl J Med*, 2017, 377(7):644-657.

[21] Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease[J]. *N Engl J Med*, 2020, 383(15):1436-1446.

[22] Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control[J]. *Nat Rev Cardiol*, 2020, 17(12):761-772.

[23] Jiang K, Xu Y, Wang D, et al. Cardioprotective mechanism of SGLT2 inhibitor against myocardial infarction is through reduction of autosis[J]. *Protein Cell*, 2021.

[24] Nahrendorf M. Myeloid cell contributions to cardiovascular health and disease[J]. *Nat Med*, 2018, 24(6):711-720.

[25] Dick SA, Macklin JA, Nejat S, et al. Self-renewing resident cardiac macrophages limit adverse remodeling following myocardial infarction[J]. *Nat Immunol*, 2019, 20(1):29-39.

[26] Sreejit G, Abdel-Latif A, Athmanathan B, et al. Neutrophil-derived S100A8/A9 amplify granulopoiesis after myocardial infarction[J].*Circulation*, 2020, 141(13):1080-1094.

[27] Toldo S, Abbate A. The NLRP3 inflammasome in acute myocardial infarction[J]. *Nat Rev Cardiol*, 2018, 15(4):203-214.

[28] Jaiswal S, Ebert BL. Clonal hematopoiesis in human aging and disease[J]. *Science*, 2019, 366(6465): eaan4673.

[29] Jaiswal S, Natarajan P, Silver AJ, et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease[J]. *N Engl J Med*, 2017, 377(2):111-121.

[30] Fuster JJ, MacLauchlan S, Zuriaga MA, et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice[J]. *Science*, 2017, 355(6327):842-847.

[31] Pascual-Figal DA, Bayes-Genis A, Díez-Díez M, et al. Clonal hematopoiesis and risk of progression of heart failure with reduced left ventricular ejection fraction[J]. *J Am Coll Cardiol*, 2021, 77(14):1747-1759.

[32] Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease[J]. *N Engl J Med*, 2017, 377(12):1119-1131.

[33] Jiang K, Tu Z, Chen K, et al. Gasdermin D inhibition confers antineutrophil-mediated cardioprotection in acute myocardial infarction[J]. *J Clin Invest*, 2022, 132(1):e151268.

[34] van Hout GP, Bosch L, Ellenbroek GH, et al. The selective NLRP3-inflammasome inhibitor MCC950 reduces infarct size and preserves cardiac function in a pig model of myocardial infarction[J]. *Eur Heart J*, 2017, 38(11):828-836.

[35] Hu JJ, Liu X, Xia S, et al. FDA-approved disulfiram inhibits pyroptosis by blocking gasdermin D pore formation[J]. *Nat Immunol*, 2020, 21(7):736-745.

[36] Mullard A. Roche snaps up another NLRP3 contender[J]. *Nat Rev Drug Discov*, 2020, 19(11):744.

[37] Larson RC, Maus MV. Recent advances and discoveries in the mechanisms and functions of CAR T cells[J]. *Nat Rev Cancer*, 2021, 21(3):145-161.

[38] Rurik JG, Tombácz I, Yadegari A, et al. CAR T cells produced *in vivo* to treat cardiac injury[J]. *Science*, 2022, 375(6576):91-96.

[39] Aghajanian H, Kimura T, Rurik JG, et al. Targeting cardiac fibrosis with engineered T cells[J]. *Nature*, 2019, 573(7774):430-433.

[40] Dutta P, Courties G, Wei Y, et al. Myocardial infarction accelerates atherosclerosis[J]. *Nature*, 2012, 487(7407):325-329.